IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

AJANI et al — Atty. Ref.: 622-96; Confirmation No. 7152

Appl. No. 10/588,272 — TC/A.U. 1619

Filed: August 4, 2006 — Examiner: Wheeler, T. M.

For: PHARMACEUTICAL OR DIETARY COMPOSITIONS BASED ON SHORT-CHAIN FATTY ACIDS AND COMPLEX SUGARS, FOR INTESTINAL DISORDERS

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION

I, Luigi Moro, hereby declare and state that:

1. I am a co-applicant of the present application.

2. I have read the outstanding Official Action and the cited prior art.

3. The present invention is based on the discovery that the combination of a short-chain fatty acid (SCFA) or a salt thereof and a complex soluble sugar and/or dietary fibre leads to a significant synergistic effect between these components which, in turn, provides beneficial effects to the patient.

4. The invention provides an oral pharmaceutical or dietary composition containing a complex sugar and/or dietary fibre selected from inulin, pectin, dextrin, maltodextrin or derivatives thereof, an active ingredient consisting of at least one short-

chain fatty acid or salt thereof, and one or more pharmacologically acceptable excipients.

5. The composition comprises a matrix consisting of lipophilic compounds with a melting point lower than 90°C and optionally amphiphilic compounds in which the active ingredient are at least partially incorporated, an amphiphilic matrix, and an outer hydrophilic matrix in which the lipophilic matrix and the amphiphilic matrix are dispersed.

6. Attached as Exhibit 1 is a copy of an experimental report performed under my direct supervision and control to evaluate the dissolution profile of the compositions of the invention, particularly tablets containing SCFA (calcium butyrate) and inulin.

7. The test was been performed according to the USP Pharmacopoeia (apparatus II, see Jinhe Li *et al.*, PharmaSciTech, December 2, 2002; 3 (4), article 33; of record in this case), without adding any triggering agent.

8. The tested tablets showed a characteristic extended dissolution profile due to the specific multi-matrix structure of the product, which can be distributed in different regions in the intestinal tract (see the experimental report and Example 4 of the present application).

8. None of the cited prior art discloses or suggests the synergistic technical effect achieved by the present invention, including the control of the release of the active through a specific multi-matrix structure of the composition.

I declare that all statements herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Luigi Moro

July 7th, 2011
Date

Exhibit 1

DEVELOPMENT TECHNICAL REPORT

Work purpose.
In order to assess a composition able to delivery the active ingredients for an extended period of time once swallowed, the formulation prototypes are subjected to a dissolution test carried out according to the Pharmacopoeia requirements and at different media pH, simulating the biological situation one tablet could encounter during the digestion by a human subject.

Materials and methods.
The dissolution test have been carried out on several batches of tablets individually containing Calcium Butyrate and Inulin, at the dose of 250mg each. The test have been performed on the coated tablets (batches 5857, 5858 and D408/1) and on the cores (batch D408F), taken as intermediate products. Different solvent compositions for the coating have been tested too (batch D408F-2/04)
The dissolution test have been carried out following the requirement of USP Pharmacopoeia, at 37±2°C, with the paddle apparatus II at 100 rpm and with a dissolution medium volume of 1.000 ml/vessel. The medium pH have been selected in order to simulate all the pH environments that a tablet swallowed could be tipically exposed to, namely pH 1, 6.4 and 7.2.

Results.
The dissolution test of batch 5857 and 5858 have been done to help the formulator to define the final product formulation; they are reported in the following Table and are useful to understand that the composition allows for a controlled release:

Batch # 5857

Vessel n°	*time 1h*	*4h*	*6h*
1	0%	15%	23%
2	0	34	41
3	0	21	31
4	0	29	37
Average	0	25	33

Batch # 5858

Vessel n°	*time 1h*	*4h*	*6h*
1	0%	17%	24%
2	0	11	18
3	0	21	30
4	0	18	28
Average	0	17	25

The information allowed to design the final formulation, which characteristics in term of dissolution are the following:

Batch # D408/1 cores

Vessel n°	*time 2h*	*4h*	*24h*
1	28%	43%	95%
2	27	41	101
3	29	61	n.d.
4	33	51	n.d.
Average	29	49	98

The application of two different solvent composition of the coating, after a check that at pH 1 and 6.4 there was no dissolution at all, was checked at pH 7.2 on these cores:

Batch # D408F-2 alcoholic coating compos.

Vessel n°	*time 2h*	*4h*	*24h*
1	2.4%	8.0%	76%
2	2.0	10.2	78
3	2.0	9.3	>70
4	1.8	8.54	>70
5	3.6	8.1	>70
6	2.1	9.1	>70
Average	**2.3**	**8.9**	**>70**

Batch # D408F-2 aqueous coating compos.

Vessel n°	*time 2h*	*4h*	*24h*
1	6.6%	17.2%	93.2%
2	6.3	20.1	93.1
3	12	25.5	>70
4	8.5	18	>70
5	6.4	18.3	>70
6	7.5	19.1	>70
Average	**7.9**	**19.9**	**>70**

Based on these pilot experiments, the final coating composition was applied with an alcoholic coating compostion and the final dissolution characteristics at pH 7.2 of two product batches are listed here below:

Batch # D408F-1

Vessel n°	*(time 2h pH 1)*	*8h pH7.2*	*24h*
1	0%	31%	>80%
2	0	26	>80
3	0	37	>80
4	0	30	>80
5	0	34	>80
6	0	33	>80
Average	**0**	**32**	**>80**

Batch # D328H .

Vessel n°	*time 4h*	*8h*	*24h*
1	9.6%	23.7%	93.2%
2	7.3	17.1	93.1
3	8.1	18.9	>80
4	10.8	26.6	>80
5	6.8	12.8	>80
6	12.5	28.6	>80
Average	**9.2**	**21.3**	**>80**

Conclusion.

The composition is able to display typical extended release characteristics.
The controlled release properties seems belonging to the core itself, where the individual characteristics of the formulation component are able to shrink or prolonge the final product dissolution performances Furthermore, the extended release characteristics are enhanced by selecting the more suitable coating composition and solvents.

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